

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

5,300

Open access books available

130,000

International authors and editors

155M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



The Importance of Vitamin D for Periodontal Tissues

Egle Jagelaviciene

Abstract

There are many causes of vitamin D deficiency, which determines pathogenesis of many diseases, including periodontal ones. Constant low uptake or deficiency of vitamin D results in progression of periodontal diseases and jaw bone metabolism - leads to change of bone mineral density, causes resorption in alveolar bone, tooth loss, changes of masticatory function and osteoporosis. The clinical studies strive to link vitamin D with gingivitis and periodontitis and prove its therapeutic and preventive role, because of vitamin D immunomodulatory, anti-inflammatory and antiproliferative effects for periodontal tissues and best treatment outcome. The purpose of this chapter is to analyze the importance of vitamin D on the pathogenesis of periodontal diseases, its role on regulation of the immune system and defense mechanism, influence on jawbone quality and on the correlation between vitamin D concentration in plasma and periodontal diseases.

Keywords: vitamin D, vitamin D deficiency, periodontal disease, jawbone, bone mineral density

1. Introduction

One billion people on the planet were diagnosed with vitamin D deficiency during the last decade [1]. Opinion, advocating important role of vitamin D and its deficiency in significant number of individuals, prevails within the society, a lot of information is available regarding its use, doses, sources, etc. However, each individual may have different vitamin D needs and the consumption of it should be monitored by testing individual serum levels of D₂ (of alimentary origin) and D₃ (synthesized in the skin), thus evaluating total level of vitamin D [2]. There are many causes of vitamin D deficiency, which is finally diagnosed if serum level of 25OHD₃ is less than 20 ng/mL [3, 4]. This determines pathogenesis of many diseases, including periodontal ones, resulting in loss of masticatory function.

Periodontium (PT) consists of gingiva, periodontal ligament, cementum and alveolar bone. This is functional unit, maintaining homeostasis – the connection between tooth and gingiva makes up a unified whole, preventing penetration of microorganisms, chemical substances, capable to induce inflammation of periodontal tissues (PTs). The periodontal ligament and bone keep tooth inside the alveolar socket, distribute mechanical load of mastication. PT has its own blood supply, neural regulation and defensive mechanisms. Soft and mineralized dental plaque is initiative risk factor of periodontal diseases (PD) – bacterial biofilm and its adhesion to tooth surface induces response of PTs, but in general, diseases are caused by many predisposing factors. PD initially manifest as gingivitis, which, if untreated, spreads

deeper within PT: causing attachment loss, periodontal pocket formation, alveolar bone resorption and tooth loss over time [5, 6]. Increasing number of studies proves importance of vitamin D in prevention and management of oral diseases [7]. Clinical studies strive to link vitamin D with PD and prove its therapeutic and preventive role. Vitamin D is secosteroidal hormone, playing important role in the treatment of gingivitis and periodontitis because of its anti-inflammatory and antibacterial effect on PTs as well as its immunomodulatory, differentiating, anti-proliferative and regulative effect on autoimmune processes, cellular apoptosis and participation in bone metabolism [3, 7–10]. Disintegration and renewal processes of bone depend on metabolism, as constant interchange of mineral substances between bone and blood plasma, where an active form of vitamin D is circulating, takes place [11]. One of the main functions of vitamin D is maintaining of blood levels of calcium and phosphorus by regulating absorption of these substances inside the bowels and reabsorption in kidneys and by enhancing remodeling processes [12, 13]. Bone is like a living and continuously changing organ where resorption and regeneration, i.e. remodeling, take place [14]. For this reason, the old bone is not accumulating and adaptation to changing mechanical forces develops. Jawbone support the teeth in alveolar sockets, skeletal bones protect internal organs and acts as depot of mineral substances especially calcium (also is necessary for normal muscle function) [15]. Osteoporotic (OP) changes of skeletal bones occur because of impaired mineralization due to long term decreased uptake of vitamin D and calcium, increasing risk of fractures, accelerated jawbone resorption causes adentia [16, 17].

2. Vitamin D metabolism

There are 4 forms of vitamin D (calciferol) – lamisterol (vit. D₁), ergocalciferol (vit. D₂), cholecalciferol (vit. D₃) and dihydrotachysterol (vit. D₄), 2 of which being the most important – D₂ and D₃. Under the influence of UV radiation, ergosterol (plant based) and cholesterol (synthesized from 7-dehydrocholesterol of animal origin) are transformed into vitamin D₂ and D₃ respectively [1, 18]. Major part of vitamin D, around 90%, is synthesized in epidermis under the effect of the sun, while the rest is absorbed in small intestine together with food, nowadays being enriched with vitamin D with increasing frequency [19, 20]. Hydroxylation of vitamin D is a two-stage process, taking place in liver and kidneys. Thus renal and liver diseases impair metabolism of vitamin D. Enzyme 25-hydroxylase transforms vitamin D₃ into 25-hydroxyvitamin D₃ 25(OH)D₃ in liver, which is the main metabolite of vitamin D₃, circulating in blood [21]. Recently it was proved that when inflammation occurs gingival fibroblasts and periodontal cells are capable of producing 25-hydroxylase and it appears to be a new extrahepatic site of 25(OH)D₃ synthesis [21]. Further, 25-hydroxyvitamin D₃ is hydroxylated in kidneys by means of 1 α -hydroxylase into 1,25-dihydroxyvitamin D (1,25(OH)₂D₃), calcitriol, active form of vitamin D, which is active hormone, participating in calcium absorption in intestines, important for both specific and nonspecific immune response against bacterial infections of oral cavity and other organs [2, 7, 21, 22]. Calcitriol binds to vitamin D-binding protein (DBP) and is transported to the cells of target tissues [23]. Synthesis of 1 α -hydroxylase starts after receptors of cellular membranes have been influenced by microorganisms. Calcitriol is activated after binding to vitamin D receptors (VDR) of nuclei of immune and epithelial cells [7, 23–25]. VDR can be found in many human tissues, regulating activity of more than 200 genes in direct or indirect way [26, 27]. Numerous distribution of VDR in tissues determines complex effect of vitamin D, whereas deficiency determines disorders [26–28]. Polymorphism of VDR gene is related to many infectious diseases, including PD

[28–30]. Polymorphism of VDR gene and exact mechanism of periodontitis remain unclear so far. There is no link established between polymorphism of VDR genes and aggressive form of periodontitis [31, 32].

3. The role of vitamin D in immune response of periodontal tissues

Marginal gingival epithelium (GE) descends from free inner margin towards root apex and transits to sulcular epithelium – semi permeable membrane. Sulcular epithelium attaches to tooth by means of loose connections, creating favorable conditions for bacterial invasion from dental plaque [33]. Thin and non-keratinized epithelium forms a junctional epithelium (JE), laying at the bottom of gingival sulcus. JE is a narrow structure of 1–2 mm with good regenerative properties, connected to tooth by layer of organic substance. Its cubic and flat cells have gaps and attach to tooth and with each other by means of hemidesmosoms and have 2 basal membranes: internal, near the tooth, and the outer one on the other side, contacting with subepithelial tissue. Disruption of the bonds between enamel cuticle and JE leads to inflammatory processes. This anatomical unit plays a barrier function, which is supported by gingival fluid, flushing gingival sulcus – blood filtrate, containing lots of various protective cells (neutrophilic leucocytes, lymphocytes, monocytes, and macrophages), specific antibodies, immunoglobulins, cytokines, proteins, enzymes, epithelial cells and bacteria. The amount of gingival fluid can change due to circadian rhythms and depends on the health of PTs, oral hygiene, mechanic impact while mastication, medications used, etc. [34, 35]. Plasma proteins strengthen junctional epithelium-enamel bonds and namely calcitriol, affecting nonspecific immunity, activates synthesis of proteins, necessary for small adherens, gap and desmosome epithelium intercellular junctions, activates hydrogen peroxide secretion in monocytes, stimulates the synthesis of antimicrobial peptides, chemotaxis, production of cytokines and chemokines, cellular reproduction, vascular permeability, wound healing, and neutralization of bacterial endotoxins [7, 25, 36]. Hence 1,25(OH)₂D₃ enhances antibacterial defense of GE [25, 36, 37].

Immune response can be nonspecific and specific. After bacteria have entered the periodontal tissues, defensive mechanism starts – immune response, during which the foreign substance is neutralized and eliminated or memorized. Neutrophilic leucocytes play important role in nonspecific immune response. It is interesting, that these cells are always found in gingival sulcus and this is the only site in organism, where neutrophilic leucocytes can freely migrate from organism outwards. During the bacterial invasion into PTs, chemotactic mechanisms are activated and neutrophilic leucocytes start migrating from blood vessels into inflamed tissues. Right here, together with macrophages, they take part in phagocytosis, thus fighting with different antigens. Neutrophilic leucocytes, monocytes and activated macrophages produce immune mediators (IL-1 β , IL-1 α , IL-6, IL-10, IL-12, TNF- α , PGE₂, MMP, Interferon γ (IFN γ)) and chemokines [37]. Vitamin D protects the organism from excessive immune response by decreasing the secretion of IL-1, IL-6, IL-8, IL-12, TNF- α cytokines, decreases production of matrix metalloproteinase (MMP) in leucocytes [33, 38]. MMP – enzymes, participating in alterations of intercellular tissues. Blood plasma levels of MMP-3, MMP-8 and MMP-9 increase with PD [39]. Very high level of MMP-9 is detected in cases of rapidly progressing periodontitis, but it can decrease up to 69% taking even little doses of vitamin D for extended period of time [40, 41].

Blood monocytes, after migration into connective tissues, transform into macrophages, which are very important for both, cellular and humoral immunity, as they have surface receptors, reacting with any foreign substance [42]. In the process

of phagocytosis, immunoglobulins and serum complement envelope foreign substance. Such formation enters phagocytic vacuoles and is destroyed by lysosome enzymes. Afterwards these substances are transferred to lymphocytes, determining further immune response [42]. Products of tissue breakdown, histamine and complement system enhances phagocytosis. Specific immune response manifests later. Antibodies circulate in blood, T and B lymphocytes react only to specific antigen. Lymphocytes are often related to Langerhans cells of oral epithelium, producing cytokines, e.g., IL-1, activating T lymphocytes, enhancing proliferation and production of antibodies. Active T lymphocytes have cytotoxic effect. Keratinocytes of oral epithelium produce IL-1 and IL-8, regulating the amount of lymphocytes and polymorphonuclear leucocytes [42]. Impaired specific immunity is responsible for resorption, osteoclast genesis and inflammatory processes of bone, thus causing autoimmune diseases. Calcitriol suppresses progression of OP and PD with signs of autoimmune diseases.

Active hormonal form of vitamin D, $1,25(\text{OH})_2\text{D}_3$, directly regulates antimicrobial immune response, modulates cytokine production and stimulates secretion of antimicrobial peptides by monocytes-macrophages and activates release of hydrogen peroxide in monocytes, thus exhibiting anti-inflammatory and antimicrobial properties [7, 43, 44]. Monocytes not only produce cytokines, but $\text{TNF-}\alpha$ as well, they release substances, activating lymphocytes and interacting with them as antigen-presenting cell (APC), destroy PTs, accelerate proliferation, differentiation and activation of osteoclasts, move in tissues in chemotactic way and participate in phagocytosis. Antimicrobial peptides play important role in nonspecific immunity against periodontitis causing agents. Antimicrobial peptides, β -defensins and especially cathelicidine LL-37 take part in neutralization of bacterial endotoxins, healing of wounds, regulate cell multiplication, blood vessel permeability, cytokine and chemokine production and chemotaxis, have prolonged antimicrobial activity and neutralize lipopolysaccharides as well [3, 7, 23, 25, 45, 46]. Activity of defensins depends on vitamin D levels [45, 46]. β -defensins show antimicrobial activity on PD bacteria– *Actinobacillus actinomycetemcomitans*, *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Candida* and papilloma viruses [47]. APCs, including macrophages and dendritic cells, transform the main $25(\text{OH})\text{D}_3$ form circulating in blood into active $1,25(\text{OH})_2\text{D}_3$, and, via VDR, induce cellular response and regulate transcription. Antimicrobial activity via VDR is associated with cathelicidine hCAP-18 gene [48]. Cathelicidine has wide antimicrobial activity against gram-positive and gram-negative bacteria, some fungi and viruses [3]. Treatment with vitamin D increases cathelicidine mRNA level in keratinocytes, neutrophils and macrophages [3, 44]. Irritation of macrophage receptors with pathogens increases synthesis of $1,25(\text{OH})_2\text{D}_3$, activity in macrophages and production of antibacterial proteins, cathelicidine and β -defensins, increases [43]. Therefore, it is supposed that vitamin D deficiency determines weak antibacterial response and tendency to infections [49].

During specific immune response, $1,25(\text{OH})_2\text{D}_3$ affects B and T lymphocytes [7]. The latter release cytokines (interleukine-1, $\text{TNF-}\alpha$, macrophage activating factor, macrophage migration inhibitory factor), stimulating resorption of dental supportive tissues (due to increased number of osteoclasts) and decay of extracellular matrix; release immunoglobulins; destroy pathogens, transferred by macrophages and dendritic cells and participate in production of antibodies. Such immune response mechanism enhances pathogenesis of PTs and aggravates the course of disease [16, 21, 33]. $1,25(\text{OH})_2\text{D}_3$ suppresses proliferation, maturation and differentiation of dendritic cells [50]. T lymphocytes are one of the dominating cells in the beginning of PTs pathologic process and its regulator; immature

dendritic cells stimulate their tolerance, whereas mature dendritic cells activate them [51]. $1,25(\text{OH})_2\text{D}_3$ decreases the number of APCs and ability of T lymphocyte to stimulate monocytes-macrophages [52]. The main target is T helpers. Vitamin D can contribute to formation of acquired immune response by selective stimulation of the specific T helpers [53]. B lymphocytes interact with macrophages and become plasmocytes, releasing Ig, which adhere to antigens. Such antigen-antibody complex activates complement system, initiating production of cytotoxic molecules, increasing blood vessel permeability, acting as chemotactic agents for polymorphonuclear leucocytes and macrophages. Vitamin D inhibits T lymphocyte proliferation, release of immunoglobulins and transformation of B lymphocytes into plasmocytes, hereby suppressing specific immune response, release of IL-1, IL-6, IL-8, IL-12 cytokines and α TNF- α [16, 21, 52]. IL-1, IL-6 and TNF- α are potential activators of osteoclasts and supporters of inflammation. IL-1 is released not only by afore mentioned monocyte-macrophages, but by endothelial and epithelial cells, fibroblasts and lymphocytes as well. This substance supports inflammation, stimulates production, differentiation and activation of osteoclasts, leading to resorption of alveolar bone, release of enzymes splitting extracellular matrix and release of E2 prostaglandin, enhancing relaxation of blood vessels and edema in PTs [13]. IL-6 activates synthesis of C reactive protein and glucose metabolism [54]. It is proven, that increase of vitamin D serum levels leads to decrease of IL-6 and leptin (factor indicating inflammation) levels, increase of adiponectin (cytokine inhibitor) and IL-8 levels [54, 55]. IL-8 activates neutrophil chemotaxis and is found in normal PTs. Its levels increase with the progression of inflammatory processes, therefore polymorphonuclear neutrophils are the first to react to inflammation. Its deficiency is related to severe forms of periodontitis. As the amount of pathogens increases, IL-8 levels and number of neutrophils increase as well, causing destruction of PTs [6]. Vitamin D acts on periopathogens, inhibits inflammation of PT and decreases IL-8 expression in periodontal ligament [55]. It can be concluded, that vitamin D plays important role in defensive mechanisms of PT and vital for the health of both soft and hard PTs.

4. Change in the concentration of 25-hydroxyvitamin D in plasma by periodontal diseases

There is no unanimous attitude towards the relation between these two factors as there exist differences between populations, test methodology and occurring limitations of the tests. When analyzing the relation between vitamin D, as protective factor, and PD, different criteria of vitamin D and examination of PTs are applied: average plasma level of vitamin D, dosage applied or any other certain diagnostic criteria. Status of PTs is evaluated according to the periodontal pocket depth, clinical attachment level, clinical attachment loss, attachment gain, alveolar bone loss, bone defects in oral cavity or any other selected criteria, such as short/long term results of periodontal surgery [56]. If only one side of oral cavity is examined, data cannot be accurate and the amount of information is lost. Studies can cover general population or part of it, e.g., smoking individuals, individuals of different age, with different PD, etc. Scientific base of linking these two factors and widening of the knowledge is possible due to widely chosen evaluative protocols and indicators. For example, smoking is risk factor for PD, but with the additional deficiency of vitamin D, destruction of PTs is more severe and more cases are identified [57]. Individuals over 50 year with low vitamin D levels have greater periodontal attachment loss than ones with high levels [58]. PTs in most cases are

healthier and risk is lower in individuals with sufficient levels of vitamin D, but it is not successfully proved in all the cases, leading to the controversial interpretation of the results obtained [56, 58–61]. It is becoming clear, that performing blood tests and monitoring vitamin D levels it is possible to suspect that individual is suffering from chronic periodontitis and condition of PTs is poor, especially in older population [56, 62, 63]. It can be one of additional diagnostic possibilities.

In case of acute inflammation, serum levels of 25-hydroxyvitamin D are increasing, as periodontal cells are producing it in the site of inflammation as anti-inflammatory agent. Serum levels of 25-hydroxyvitamin D usually are lower in cases of chronic inflammation. Such correlation might be explained that because of low serum levels of vitamin D, ability of epithelium to fight against pathogens is impaired and inflammation develops. Optimal serum level of 25-hydroxyvitamin D for prophylactic and therapeutic purposes should be 90-100 nmol/l, but it is not definitely clear what should be the daily dose of vitamin D in order to achieve these levels [13]. Gingival bleeding are the sign of both, acute and chronic PD. Decreased level of 25-hydroxyvitamin D correlates with worsened health status of PTs; course of chronic gingivitis (with insufficient serum levels) and intensified gingival bleeding [36, 58]. Gingival bleeding during the probing is observed by 20% less in patients with high serum levels of 25(OH)D, those with sufficient (≥ 50 nmol/L) levels of vitamin are less likely to develop PD by 33% and by 42% are less likely to have more than 50% of gingival bleeding [60, 64]. Prolonged combined supplementation of vitamin D and calcium decreases bleeding on probing, changes the clinical attachment level and pockets depth [65]. The tendency to severe periodontitis may decrease up to 33% with daily dose of 800 IU of vitamin D [62]. Exacerbation of gingival bleeding is observed during pregnancy, thus there are data, concerning the influence of vitamin D during this period (if 25(OH)D level < 75 nmol/L) [36]. Without timely evaluation of all these data, periodontitis of more severe form develops, as correlation between increased serum levels of vitamin D₃ and severity of PD exists, though it is not always confirmed [36, 66, 67]. There are cases described when serum level of 1,25(OH)D increases significantly following the periodontal treatment [68]. Besides, increased serum level of 25(OH)D is common in patients with aggressive periodontitis (AP)- disease of PTs, affecting young individuals, characterized by rapid destruction of PT and tooth loss. Significantly higher vitamin D binding protein (DBP), IL-6, procalsitonine and 25(OH)D₃ plasma levels and higher counts of leucocytes and neutrophils are found in patients with this PD [69]. Level of 25(OH)D₃ increases due to activation of 25-hydroxylase in periodontal cells in acute inflammation of PTs, and decrease in chronic one [67]. Due to production of this enzyme in cases of AP, levels of 25(OH)D₃ in gingival sulcus is up to 300 times higher than in blood plasma [21]. DBP is plasma protein and is synthesized by hepatocytes [70]. It is the main carrier of 25(OH)D₃ in the plasma, directly affecting cellular functions, including activity of macrophages [71, 72]. DBP bound to the cell surface, B-lymphocytes, T-lymphocytes, monocytes, neutrophils [70]. The amount of this protein is related to the severity degree of illness with direct relation to neutrophil – increased number of neutrophils and IL-6 can contribute to increased plasma levels of DBP by active periodontitis. DBP is the most important “during inflammation since it induces selective recruitment of neutrophils” [70]. Activated neutrophils can excrete DBP, which expression is regulated by IL-6, participating in immune response [69]. Thus detection of plasma levels of DBP could confirm correlation between it and periodontal inflammation. Anti-inflammatory effect depends on the dose of vitamin supplement. Safe and effective anti-inflammatory dose of 500–2000 IU of vitamin D is recommended. Results are noted earlier when higher dose of 2000 IU is used [73].

5. Conclusion

In conclusion, vitamin D is very unique substance due to its abilities, functions and participation in various processes. Its optimal serum levels could prevent occurrence of numerous diseases, including such common diseases throughout the world as chronic periodontal diseases, which are social problems, compromising individual's quality of life.

Conflict of interest

The author declares no conflict of interest.

Author details

Egle Jagelaviciene
Department of Dental and Oral Pathology, Lithuanian University of Health
Sciences (LUHS), Kaunas, Lithuania

*Address all correspondence to: egle.jagelaviciene@lsmuni.lt

IntechOpen

© 2021 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] Gailytė I. Jaunų sveikų vyrų vitamino D koncentracijos, kūno sandaros, endokrininės ir psichologinės būklės bei gyvenimo kokybės sąsajos (Associations Between Vitamin D Concentration, Body Composition, Endocrine and Psychological State and Life Quality in Young Healthy Men. [thesis]. Kaunas, Lietuvos Sveikatos Mokslų Universitetas; 2013.
- [2] Holman P. Vitamin D Day November 2nd – Help Stop Vitamin D Deficiency. Woodstock. 2013.10.31
- [3] Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology & Metabolism*. 2011;96(7):1911-30. DOI: 10.1210/jc.2011-0385
- [4] Glade MJ. Vitamin D: Health panacea or false prophet? *Nutrition* 2013;29:37-41. DOI: 10.1016/j.nut.2012.05.010
- [5] Amin E. Hatem. Epidemiology and Risk Factors of Periodontal Disease. In *Intechopen.com/books*, editor. 2011;03:213-222. DOI:10.5772/29272
- [6] Bikle DD. Vitamin D and the immune system: Role in protection against bacterial infection. *Current Opinion in Nephrology and Hypertension*. 2008;17: 348-352. DOI: 10.1097/MNH.0b013e3282ff64a3
- [7] Schwalfenberg GK. A review of the critical role of vitamin D in the functioning of the immune system and the clinical implications of vitamin D deficiency. *Molecular Nutrition & Food Research*. 2011 Jan;55(1):96-108. DOI: 10.1002/mnfr.201000174
- [8] Muszkat P, Camargo MB, Griz LH, Lazaretti-Castro M. Evidence-based non-skeletal actions of vitamin D. *Arquivos Brasileiros de Endocrinologia & Metabologia*. 2010;54(2):110-7. DOI: 10.1590/s0004-27302010000200005.
- [9] Krishnan AV, Feldman D. Mechanisms of the anti-cancer and antiinflammatory actions of vitamin D. *Annual Review of Pharmacology and Toxicology*. 2011;51:311-36. DOI: 10.1146/annurev-pharmtox-010510-100611.
- [10] Gropper SS, Smith JL, Groff JL, editors. *Advanced Nutrition and Human Metabolism*. 5. Belmont, CA: Wadsworth, Cengage Learning; 2009. Calcium; p. 431-443.
- [11] Praškevičius A, Burneckienė J. Kaulų, dantų, seilių biochemija (Biochemistry of bones, teeth and saliva). Kaunas: KMU Press; 2000. p.44.
- [12] Amano Y, Komiyama K, Makishima M. Vitamin D and periodontal disease. *Journal of Oral Science*. 2009 Mar;51(1):11-20. DOI: 10.2334/josnurd.51.11
- [13] Hildebolt CF. Effect of vitamin D and calcium on periodontitis. *Journal of Periodontology*. 2005 Sep;76(9):1576-87. DOI: 10.1902/jop.2005.76.9.1576.
- [14] Lopata G. Dabartinis požiūris į kaulinio audinio remodeliaciją (Current approaches to bone remodeling). *Lietuvos endokrinologija*. 2003;11(1,2,3):82-8.
- [15] Berchtold MW, Brinkmeier H, Muntener M. Calcium ion in skeletal muscle: its crucial role for muscle function, plasticity, and disease. *Physiological Reviews*. 2000;80(3):1215-65. DOI: 10.1152/physrev.2000.80.3.1215
- [16] Stein SH, Tipton DA. Vitamin D and its impact on oral health-an update. *The Journal of the Tennessee Dental Association*. 2011 Spring;91(2):30-3; quiz 34-5.

- [17] Palacios C, Joshipura K, Willett W. Nutrition and health: guidelines for dental practitioners. *Oral Dis.* 2009 Sep;15(6):369-81. DOI:10.1111/j.1601-0825.2009.01571.
- [18] Available from: https://lt.wikipedia.org/wiki/Vitamin_D[internet]. [Accessed: 2020.12.20]
- [19] Zittermann A, Gummert J F. Nonclassical Vitamin D Action. *Nutrients* 2010, 2(4), 408-425. DOI:10.3390/nu2040408
- [20] DeLuca HF. Overview of general physiologic features and functions of vitamin D. *American Journal of Clinical Nutrition.* 2004;80 (6 Suppl):1689S–96S. DOI: 10.1093/ajcn/80.6.1689S
- [21] Liu K, Meng H, Hou J. Activity of 25-hydroxylase in human gingival fibroblasts and periodontal ligament cells. *PLoS One.* 2012;7(12):e52053. DOI: 10.1371/journal.pone.0052053
- [22] Bikle DD. Vitamin D Metabolism and Function in the Skin. *Molecular and Cellular Endocrinology.* 2011 Dec 5; 347(1-2): 80-89. DOI: 10.1016/j.mce.2011.05.017
- [23] Chun RF, Adams JS, Hewison M. Back to the future: a new look at ‘old’ vitamin D. *Journal of Endocrinology.* 2008;198(2):261-9. DOI: 10.1677/JOE-08-0170
- [24] Van der Velden U, Kuzmanova D, Chapple I.L. Micronutritional approaches to periodontal therapy. *J. Clin.Periodontol.* 2011; 38 (Suppl. 11), 142-158. DOI: 10.1111/j.1600-051X.2010.01663.x
- [25] McMahon L, Schwartz K, Yilmaz O, Brown E, Ryan LK, et al. Vitamin D-mediated induction of innate immunity in gingival epithelial cells. *Infection and Immunity.* 2011;79:2250-2256. DOI: 10.1128/IAI.00099-11
- [26] Nagpal S, Na S, Rathnachalam R. Noncalcemic actions of vitamin D receptor ligands. *Endocrine Reviews.* 2005;26(5):662-87. DOI: 10.1210/er.2004-0002
- [27] Holick MF. Vitamin D deficiency. *New England Journal of Medicine.* 2007;357:266-281.
- [28] Bellamy, R, Ruwende, C, Corrah T, McAdam K P, Thursz M, Whittle H C, Hill A V. Tuberculosis and chronic hepatitis B virus infection in Africans and variation in the vitamin D receptor gene. *Journal of Infectious Diseases.* 1999; 179, 721-724. DOI: 10.1086/314614
- [29] Park K S, Nam J H, Choi J. The short vitamin D receptor is associated with increased risk for generalized aggressive periodontitis. *Journal of Clinical Periodontology.* 2006; 33, 524-528. DOI. org/10.1111/j.1600-051X.2006.00944.x
- [30] de Brito Junior R B, Scarel-Caminaga R M, Trevilatto P C, de Souza A P, Barros S P. Polymorphisms in the vitamin D receptor gene are associated with periodontal disease. *Journal of Periodontology.* 2004; 75, 1090-1095. DOI: 10.1902/jop.2004.75.8.1090
- [31] Deng H1, Liu F, Pan Y, Jin X, Wang H, Cao J. BsmI, TaqI, ApaI, and FokI polymorphisms in the vitamin D receptor gene and periodontitis: a meta-analysis of 15 studies including 1338 cases and 1302 controls. *Clinical Periodontology.* 2011;38(3):199-207. DOI: 10.1111/j.1600-051X.2010.01685.x
- [32] Li-li Chen,* Hao Li,† Peng-peng Zhang,* and Shu-mei Wang* Association Between Vitamin D Receptor Polymorphisms and Periodontitis: A Meta-Analysis. *Journal of Periodontology* 2012;83:1095-1103. DOI: 10.1902/jop.2011.110518
- [33] Jagelaviciene E, Vaitkeviciene I, Silingaite D, Sinkunaite E, Daugelaite G. The Relation between Vitamin D and

Periodontal Pathology. Medicina 2018; 55(2). DOI: 10.3390/medicina54030045

[34] Newman MG, Takei HH, Carranza FA. Carranza's Clinical Periodontology. 9th ed. W.B. Saunders company, USA; 2002.

[35] Vaitkeviciene I, Jagelaviciene E, Vaitkevicius R. Įvadas į periodontologijos kursą (Introduction to the course of periodontology). LSMU, Leidybos namai, Kaunas, 2019.

[36] Boggess KA, Espinola JA, Moss K, Beck J, Offenbacher S, Camargo CA Jr Vitamin D status and periodontal disease among pregnant women. Journal of Periodontology. 2011 Feb;82(2):195-200. DOI: 10.1902/jop.2010.100384

[37] Kornman K S, Page R C, Tonetti M S. The host response to the microbial challenge in periodontitis: assembling the players. Periodontology 2000. 1997 Jun;14:33-53. DOI: 10.1111/j.1600-0757.1997.tb00191.x

[38] Coussens A, Timms PM, Boucher BJ, Venton TR, Ashcroft AT, Skolimowska KH, et al. 1 α ,25-dihydroxyvitamin D₃ inhibits matrix metalloproteinases induced by *Mycobacterium tuberculosis* infection. Immunology 2009; 127:539-48. DOI: 10.1111/j.1365-2567.2008.03024.x

[39] Marcaccini AM, Novaes AB Jr, Meschiari CA, Souza SL, Palioto DB, Sorgi CA, et al. Circulating matrix metalloproteinase-8 (MMP-8) and MMP-9 are increased in chronic periodontal disease and decrease after non-surgical periodontal therapy. Clinica Chimica Acta 2009; 409:117-22. DOI: 10.1016/j.cca.2009.09.012

[40] Lorencini M, Silva JA, de la Hoz CL, Carvalho HF, Stach-Machado DR. Changes in MMPs and inflammatory cells in experimental gingivitis. Histology and Histopathology. 2009; 24:157-66. DOI: 10.14670/HH-24.157

[41] Timms PM, Mannan N, Hitman GA, Noonan K, Mills PG, Syndercombe-Court D, et al. Circulating MMP9, vitamin D and variation in the TIMP-1 response with VDR genotype: mechanisms for inflammatory damage in chronic disorders? QJM: An International Journal of Medicine. 2002;95:787-96. DOI.org/10.1093/qjmed/95.12.787

[42] Vaitkeviciene I, Jagelaviciene E, Vaitkevicius R. Burnos gleivinė: sandara, funkcijos ir tyrimas (Oral mucosa: structure, functions and examination). LSMU, Leidybos namai, Kaunas, 2015.

[43] Liu PT, Stenger S, Li H et al. Toll-like receptor triggering of a vitamin D-mediated human anti-microbial response. Science 2006;311:1770-1773. DOI: 10.1126/science.1123933

[44] Wang TT, Nestel FP, Bourdeau V et al. Cutting edge: 1, 25-dihydroxyvitamin D₃ is a direct inducer of antimicrobial peptide gene expression. Journal of Immunology. 2004;173:2909-2912. DOI: 10.4049/jimmunol.173.5.2909

[45] Weber G, Heilborn JD, Chamorro Jimenez CI. et al. Vitamin D induces the antimicrobial protein hCAP18 in human skin. Journal of Investigative Dermatology. 2005;124:1080-1082. DOI: 10.1111/j.0022-202X.2005.23687.x

[46] Yim S, Dhawan P, Ragunath C, Christakos S, Diamond G. Induction of cathelicidin in normal and CF bronchial epithelial cells by 1,25-dihydroxyvitamin). Journal of Cystic Fibrosis. 2007;6:403-410. DOI: 10.1016/j.jcf.2007.03.003

[47] Zhou C, Assem M, Tay JC, Watkins PB, Blumberg B, Schuetz EG, Thummel KE 2006 Steroid and xenobiotic receptor and vitamin D receptor crosstalk mediates CYP24 expression and drug-induced

osteomalacia. *Journal of Clinical Investigation* 116:1703-1712. DOI: 10.1172/JCI27793

[48] Martineau AR, Wilkinson KA, Newton SM et al. IFN gamma and TNF-independent vitamin D-inducible human suppression of mycobacteria: the role of cathelicidin LL-37. *Journal of Immunology*. 2007;178:7190-7198. DOI: <https://doi.org/10.4049/jimmunol.178.11.7190>

[49] Hewison M. Antibacterial effects of vitamin D. *Nature Reviews Endocrinology*. 2011;7:337-345. DOI: 10.1038/nrendo.2010.226

[50] Gauzzi MC, Purifatto C, Donato K et al. Suppressive effect of 1 alpha,25-hydroxyvitamin D3 on type I IFN-mediated monocyte differentiation into dendritic cells: impairment of functional activities and chemotaxis. *Journal of Immunology*. 2005;174:270-276. DOI: 10.4049/jimmunol.174.1.270

[51] Abiko Y, Saitoh M, Nishimura M, Yamazaki M, Sawamura D, Kaku T (2007) Role of β -defensins in oral epithelial health and disease. *Medical Molecular Morphology*. 40, 179-184.

[52] Almerighi C, Sinistro A, Cavazza A et al. 1a,25-hydroxyvitamin D3 inhibits CD-40L-induced pro-inflammatory and immunomodulatory activity. *Cytokine*. 2009;45:190-197. DOI: 10.1016/j.cyto.2008.12.009

[53] Nithya Anand, S. C. Chandrasekaran, and Narpat Singh Rajput. Vitamin D and periodontal health: Current concepts. *Journal of Indian Society of Periodontology*. 2013 May-Jun; 17(3): 302-308. DOI: 10.4103/0972-124X.115645

[54] Teles FR, Teles RP, Martin L, Socransky SS, Haffajee AD. Relationships among interleukin-6, tumor necrosis factor- α , adipokines, vitamin D, and chronic periodontitis.

Journal of Periodontology. 2012 Sep;83(9):1183-91. DOI: 10.1902/jop.2011.110346

[55] Tang X, Pan Y, Zhao Y. Vitamin D inhibits the expression of interleukin-8 in human periodontal ligament cells stimulated with *Porphyromonas gingivalis*. *Archives of Oral Biology*. 2013 Apr;58(4):397-407. DOI: 10.1016/j.archoralbio.2012.09.010

[56] Pinto JPNS, Goergen J, Muniz FWMG, Haas AN. Vitamin D levels and risk for periodontal disease: A systematic review. *Journal of Periodontal Research*. 2018;1-8. DOI: 10.1111/jre.12531

[57] Lee HJ, Je DI, Won SJ, Paik DI, Bae KH. Association between vitamin D deficiency and periodontal status in current smokers. *Community Dentistry and Oral Epidemiology*. 2015;43:471-478. DOI: 10.1111/cdoe.12173

[58] Dietrich T, Joshipura KJ, Dawson-Hughes B, Bischoff-Ferrari HA. Association between serum concentrations of 25-hydroxyvitamin D3 and periodontal disease in the US population. *American Journal of Clinical Nutrition*. 2004;80:108-113. DOI: 10.1093/ajcn/80.1.108

[59] Millen AE, Andrews CA, LaMonte MJ, et al. Vitamin D status and 5-year changes in periodontal disease measures among postmenopausal women: the Buffalo OsteoPerio Study. *Journal of Periodontology*. 2014;85:1321-1332. DOI: 10.1902/jop.2014.130686

[60] Millen AE, Hovey KM, LaMonte MJ, et al. Plasma 25-hydroxyvitamin D concentrations and periodontal disease in postmenopausal women. *Journal of Periodontology* 2013;84:1243-1256. DOI: 10.1902/jop.2012.120445

[61] Zhan Y, Samietz S, Holtfreter B, Hannemann A, Meisel P, Nauck M, Völzke H, Wallaschofski H, Dietrich T,

Kocher T. Prospective Study of Serum 25-hydroxy Vitamin D and Tooth Loss. *J Dent Res*. 2014 Jul; 93(7): 639-644. DOI: 10.1177/0022034514534985

[62] Alshouibi EN, Kaye EK, Cabral HJ, Leone CW, Garcia RI. VitaminD and periodontal health in older men. *Journal of Dental Research*. 2013;92:689-693. DOI: 10.1177/0022034513495239

[63] Wang Y, Sugita N, Yoshihara A, et al. Peroxisome proliferator-activated receptor (PPAR) γ polymorphism, vitamin d, bone mineral density and periodontitis in postmenopausal women. *Oral Dis*. 2013;19:501-506. DOI: 10.1111/odi.12032

[64] Dietrich T, Nunn M, Dawson-Hughes B, Heike A, Bischoff-Ferrari H. Association between serum concentrations of 25-hydroxyvitamin D and gingival inflammation. *American Journal of Clinical Nutrition*. 2005;82:575-80. DOI: 10.1093/ajcn.82.3.575

[65] Garcia MN, Hildebolt CF, Miley DD, Dixon DA, Couture RA, et al. One-year effects of vitamin D and calcium supplementation on chronic periodontitis. *Journal of Periodontology*. 2011; 82: 25-32. DOI: 10.1902/jop.2010.100207

[66] Liu K, Meng H, Lu R, Xu L, Zhang L, Chen Z, Shi D, Feng X, Tang X. Initial periodontal therapy reduced systemic and local 25-hydroxyvitamin D(3) and interleukin-1 β in patients with aggressive periodontitis. *Journal of Periodontology*. 2010 Feb;81(2):260-6. DOI: 10.1902/jop.2009.090355

[67] Liu K, Meng H, Tang X, Xu L, Zhang L, et al. Elevated plasma calcifediol is associated with aggressive periodontitis. *Journal of Periodontology*. 2009;80: 1114-1120. DOI: 10.1902/jop.2009.080675

[68] Antonoglou G, Knuuttila M, Niemelä O, Hiltunen L, Raunio T, Karttunen R, Vainio O, Ylöstalo P, Tervonen T. Serum 1,25(OH)D Level Increases After Elimination of Periodontal Inflammation in T1DM Subjects. *Journal of Clinical Endocrinology and Metabolism*. 2013; 98: 3999-4005. DOI: 10.1210/jc.2013-1906

[69] Zhang X, Meng H, Sun X, Xu L, Zhang L, Shi D, et al. Elevation of vitamin D-binding protein levels in the plasma of patients with generalized aggressive periodontitis. *Journal of Periodontal Research*. 2013 Feb;48(1):74-9. DOI: 10.1111/j.1600-0765.2012.01505.

[70] Richard R. Kew. The Vitamin D Binding Protein and Inflammatory Injury: A Mediator or Sentinel of Tissue Damage? *Frontiers in Endocrinology (Lausanne)*. 2019 Jul 10;10:470. DOI: 10.3389/fendo.2019.00470

[71] Speeckaert M, Huang G, Delanghe JR, Taes YE. Biological and clinical aspects of the vitamin D binding protein (Gc-globulin) and its polymorphism. *Clinica Chimica Acta* 2006;372:33-42. DOI: 10.1016/j.cca.2006.03.011

[72] White P, Cooke N. The multifunctional properties and characteristics of vitamin D-binding protein. *Trends Endocrinol Metab* 2000;11:320-327. DOI: 10.1016/s1043-2760(00)00317-9

[73] Hiremath VP, Rao CB, Naiak V, Prasad KV. Anti-inflammatory effect of vitamin D on gingivitis: a dose response randomised controlled trial. *Indian J Public Health*. 2013 Jan-Mar;57(1):29-32. DOI: 10.4103/0019-557X.111365